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2007 YEAR-END SUMMARY REPORT
Associate Professor Joseph Urban, Chemistry Department

TITLE: Molecular Modeling Studies of Fluorinated Peptide and Amino Acid Analogs

The specific aims of this work are the study of fluorinated peptide mimetics and fluorinated amino acids. NARC funding in the amount of 12.5 days was provided in support of this work during the Summer of 2007. This time was roughly equally divided between continuing work on the hydrogen bonded dimer complexes of fluoroalkene model compounds (fluoroethylene and 2-fluoro-2-butene) and beginning preliminary studies of fluorinated and hydroxylated amides as models for peptidomimetics. The details of these studies and how they fit into the larger context of the entire research program can be found in the detailed proposal (Enclosure (1)). A synopsis of the key results found during the support time is presented below.

Fluoroalkene Dimers

Computational studies with a combination of ab initio and density functional methods were carried out on fluoroalkene analogs to the hydrogen bonding dimers exhibited by formamide and N-methylacetamide. The software used was GaussView 3.0 and Gaussian03 (rev. D) with calculations performed on local workstations as well as on clusters at the DoD HPC center at WPAFB, Ohio. Input structures for the fluoroalkene dimers were generated from those found previously[1] for the corresponding amide dimers. However, as can be seen in Figure 1, optimization typically led to very different structures for the fluorinated peptidomimetics. For example, stacked structures, which are not seen for the amides, are found to predominate for the peptidomimetics. These results indicate that replacement of a peptide bond by a fluoroalkene may have a significant impact on the conformational preferences of the resulting peptidomimetics. The next phase of this work is to examine the effect of solvent on the dimer structures. This will be accomplished with the use of continuum solvation models.

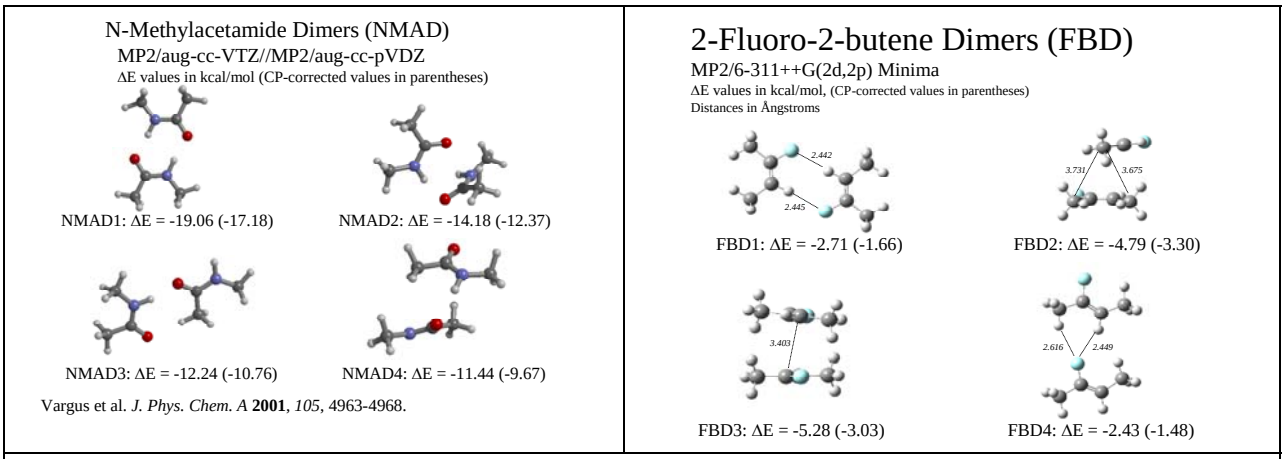

Figure 1: Structures and binding energies for amide dimers (left) compared to those of fluoroalkene dimers (right). The amide results are published result of Vargus et al.[1]

N-Hydroxy and N-Fluorinated Amides

Preliminary work was begun on prototypical hydroxylated and fluorinated amides including derivatives of formamide and N-methylacetamide. Calculations were performed with ab initio and density functional methods. The levels of theory employed were HF, MP2, and B3LYP with basis sets ranging from 6-31G(d) to aug-cc-pVTZ.

The results obtained thus far indicate that the preferred geometry of both the fluorinated and hydroxylated amides is pyramidal at nitrogen. Representative structures are shown in Figure 2. In addition, optimizations of structures that were constrained to planarity were typically found to be transitions states upon completion of the frequency calculations. This is in sharp contrast to what is seen for the amides lacking the hydroxyl or fluoro substituent. For those compounds (formamide and N-methylacetamide), all calculations led to planar minima as the lowest-energy structures, as expected. The potential energy surfaces were explored extensively (Figure 3 gives a sampling of the input geometries tested). The pyramidal structures that were obtained were found to contain imaginary frequencies indicating that they are rotational transition states.

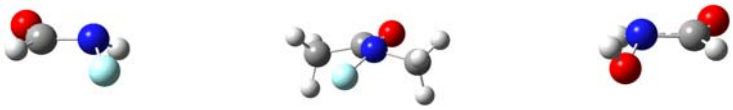

Figure 2: HF/6-31G(d) optimized structures of N-fluorinated (left and center) and N-hydroxylated (right) amides. The lowes-energy structures are found to possess pyramidal nitrogens.

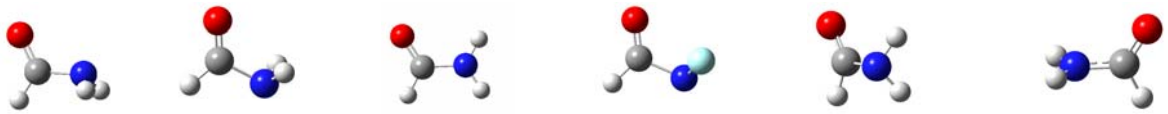

Figure 3: Input geometries investigated for N-fluoro amide compounds. The figure shows the geometries for formamide; analogous structures were generated for the N-methylacetamide series as well.

The future directions for this work include extending the studies to larger systems and examining the effect of solvent on the nitrogen inversion barriers and the conformational preferences.

(1) Vargas, R.; Garza, J.; Friesner, R. A.; Stern, H.; Hay, B. P.; Dixon, D. A. *J. Phys. Chem. A* **2001**, *105*, 4963.